

Skin tests in urticaria/angioedema and flushing to Pfizer-BioNTech SARS-CoV-2 vaccine: Limits of intradermal testing

To the Editor,

Vaccination seems the most effective public health tools to contrast the spreading of Coronavirus disease-19 (COVID-19) pandemic. To date, the European Medicines Agency (EMA) authorized three anti-SARS-CoV-2 vaccines. The Pfizer-BioNTech and the Moderna vaccines contain messenger RNA (mRNA) encapsulated in lipid nanoparticles, which encodes the SARS-CoV-2 viral spike (S) protein, inducing both antibody and cell-mediated responses. The AstraZeneca vaccine is based on a viral vector that uses a modified version of the chimpanzee adenovirus to provide instructions for synthesizing SARS-CoV-2 protein S. The vaccine series consists of two doses administered intramuscularly (Pfizer-BioNTech: 21 days apart; Moderna: 28 days apart; AstraZeneca: 28–84 days apart).

During clinical approval studies and early post-marketing phases, mucous-cutaneous adverse reactions have been rarely observed. Among hypersensitivity reactions, immediate reactions (anaphylaxis, urticaria-angioedema syndrome) were more frequently observed than delayed reactions (maculo-papular eruptions).^{1,2}

The anti-SARS-CoV-2 vaccines contain excipients with known sensitizing potential: Pfizer-BioNTech vaccine contains polyethylene glycol-2000, Moderna vaccine polyethylene glycol-2000 and tromethamine and AstraZeneca vaccine polysorbate 80.³

Considering this, before receiving anti-SARS-CoV-2 vaccination, an adequate medical history is mandatory to detect possible risk factors and, consequently, to minimize the incidence of adverse reactions. Furthermore, it is recommended to administer

the vaccine by trained healthcare personnel in adequate medical settings in presence of emergency drugs and an observation period.^{3,4}

In General Hospital of Perugia and in Local Health Unit 1, Umbria Region, Italy, 5574 healthcare professional received the first dose of Pfizer-BioNTech vaccine. Six subjects (0.11%) without previous drug hypersensitivity or polyethylene glycol reactions developed mucous-cutaneous adverse reactions, summarized in Table 1.

These patients underwent an allergologic workup with Pfizer-BioNTech vaccine as suggested by EAACI⁴ and German allergy centres.⁵ In absence of standardized methodology for this vaccine testing, we referred to Italian⁶ and EAACI recommendations.⁷ Unusable vaccine residues, regain from the vaccine campaign, were used under sterile conditions within 6 hours from reconstitution and according to the storage conditions. Skin prick test (SPT) with neat vaccine (reading: 20 min) and intradermal test (IDT) vaccine dilution 1/100 (readings: 20 min, 24 h) were performed. SPT resulted always negative, but IDT induced, 12 hours after, an erythematous, oedematous and infiltrated asymptomatic reaction in all patients. A 1/1000 dilution test induced the same reaction in all patients (Figure 1A). We followed the patients daily until resolution, and the IDT reactions persisted for 2 days. All patients then received the second dose of vaccine without relapses.

In order to verify these reactions, IDT with 1/1000 and 1/100 Pfizer-BioNTech vaccine dilution was performed in six healthcare

TABLE 1 Patients characteristic and adverse mucous-cutaneous reactions in 6 patients after the first dose of Pfizer-BioNTech vaccine

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	Female	Female	Male	Female	Female	Female
Age	24	31	28	58	44	54
Personal atopy	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis and asthma	Allergic rhinitis	Allergic rhinitis, atopic dermatitis
Allergy history	-	-	-	-	-	Contact allergy (nickel sulphate, fragrances)
Type of reaction	Generalized acute urticaria	Angioedema (tongue, gums)	Generalized acute urticaria	Flushing of the face	Flushing of the face	Angioedema (tongue, lips)
Time of onset	5 min	24 h	5 min	30 min	20 min	10 min
Treatment	Betametasone sodium phosphate (IV)	-	-	-	-	-

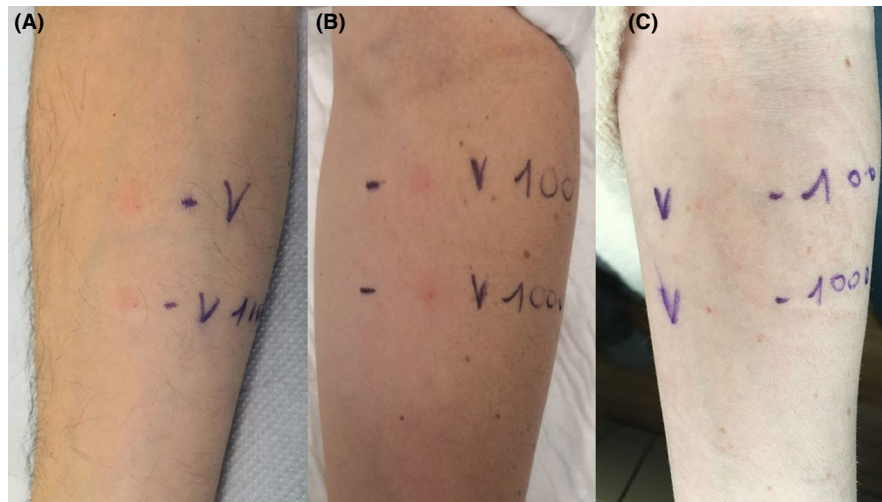


FIGURE 1 Intradermal test (IDT) with Pfizer-BioNTech vaccine. Erythematous, oedematous and infiltrated reaction at 24 h inpatient 1 (A) and in a healthcare volunteer who had received the first dose of Pfizer-BioNTech vaccine (B). Negative IDT in a not-vaccinated volunteer (C)

volunteers who had received the two doses of Pfizer-BioNTech vaccine, in six healthcare volunteers who had received at least 2 weeks before only the first dose of Pfizer-BioNTech vaccine and in six volunteers who did not receive Pfizer-BioNTech vaccine. All the 18 volunteers did not refer previous allergy to vaccines or drugs containing polyethylene glycols. IDT induced the same reaction 12 h after in the 12 vaccinated volunteers (Figure 1B), while resulted negative in the six not-vaccinated volunteers (Figure 1C). The six volunteers who had received only the first dose were then vaccinated with the second dose without problem. All patients and controls have provided an informed consent to perform these skin tests.

Even if the morphology of the IDT reactions could suggest a type IV a immune reaction that IDT reactions observed in patients and vaccinated volunteers could be a sign of desired cellular immune protection rather than an allergy to SARS-CoV-2 viral S protein or to vaccine components. This hypothesis was confirmed by the lack of relapses of mucous-cutaneous adverse reactions after second vaccine administration.

It is impossible to draw conclusions about the utility of immediate readings of SPT and IDT to investigate anaphylaxis to Pfizer-BioNTech vaccine, but for purely cutaneous reactions, they have not shown positive results in six patients and IDT has a high risk of positive delayed reactions due to cellular immune protection.

Further studies are needed to investigate the utility of SPT and IDT to investigate Pfizer-BioNTech vaccine allergy and to better clarify the pathomechanism of the reactions observed to IDT.

KEYWORDS

adverse drug reaction, intradermal test, SARS-CoV-2 vaccine, skin test

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None.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

PATIENTS CONSENT STATEMENT

All patients and controls give their consent to the skin test and to the data publication.

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REFERENCES

- Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. *JAMA* 2021;325(8):780.
- Center for Disease Control and Prevention. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine – United States; December 14–23, 2020. <https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm>. Accessed February 17, 2021.
- Caballero ML, Quirce S. Excipients as potential agents of anaphylaxis in vaccines: analyzing the formulations of the current

- authorized COVID-19 vaccines. *J Invest Allergol Clin Immunol*. 2021;31(1):92–93. <https://doi.org/10.18176/jiaci.0667>
- Sokolowska M, Eiwegger T, Ollert M, et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. *Allergy*. 2021;76(6):1629–1639.
 - Worm M, Bauer A, Wedi B, et al. Practical recommendations for the allergological risk assessment of the COVID-19 vaccination - a harmonized statement of allergy centers in Germany. *Allergol Select*. 2021;26(5):72–76.
 - Stingeni L, Bianchi L, Tramontana M, et al. Skin tests in the diagnosis of adverse drug reactions. *G Ital Dermatol Venereol*. 2020;155(5):602–621.
 - Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013;68(6):702–712.

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Ovomucoid-specific IgD increases in children who naturally outgrow egg allergy in a cross-sectional study

To the Editor,

It has been shown that egg-allergic children have higher ovomucoid (OVM)-specific IgD (sIgD) levels compared to atopic controls.¹ Within egg-allergic children, those with higher levels of OVM-sIgD have a decreased risk of anaphylaxis. A study in patients undergoing egg oral immunotherapy (OIT) demonstrated that ovalbumin (OVA)-sIgD levels increase in egg-allergic children desensitized by OIT, but not in children unresponsive to OIT or with sustained unresponsiveness to OVA challenge.² The natural development of tolerance and the acquisition of sustained unresponsiveness due to OIT in egg-allergic children are associated with an increase in OVM-specific IgG4 (sIgG4) levels and a decrease in OVM-specific IgE (sIgE) levels.³ In this cross-sectional study, we elucidated the potential role of IgD in the outgrowing of egg allergy by analyzing egg white (EW)-, OVM-, and OVA-sIgD and sIgG4 levels in sera from 57 egg-allergic children and 23 healthy non-egg-allergic children (non-egg allergy: NEA) (Table S1). Of the egg-allergic children, 28 avoided all forms of egg in the diet (complete avoidance of egg: CAE), 18 were able to ingest at least 1/32 cooked whole egg (194 mg protein) but not one cooked whole egg (3200 mg protein; partial avoidance of egg: PAE), and 11 outgrew egg allergy (OGE). The sample size was chosen based on similar previous analyses.^{1,4} The study was approved by The Research Ethics Committee of University of Fukui (#20110052), and written informed consent was obtained from the parent or guardians.

EW- and OVM-sIgE levels measured using ImmunoCAP (Thermo Fisher Inc., MA) were higher in the CAE group, followed by the PAE, OGE, and NEA groups (Figure 1, Figure S1). The CAE group exhibited lower serum levels of EW- and OVA-sIgD compared to the NEA group and the PAE group, respectively, and had the lowest OVM-sIgD serum levels among all groups, suggesting that OVM-sIgD levels are associated with outgrowing egg allergy. We observed the lowest serum levels of EW-, OVA-, and OVM-sIgG4 in the CAE group, followed by the PAE and OGE groups. The ratio of OVM-sIgD to OVA-sIgD increased as children outgrew egg allergy, while the ratio

of OVM-sIgG4 to OVA-sIgG4 did not change (Figure S2). Thus, the production of OVM-sIgD differs from OVM-sIgG4 as children naturally outgrow egg allergy.

High-affinity, but not low-affinity IgE is known to cause anaphylaxis.⁵ High-affinity IgE is derived from memory IgG1⁺ B cells without further affinity maturation, whereas low-affinity IgE is derived from naïve IgM⁺IgD⁺ B cells. Considering class switching pathways and affinity maturation, elevated OVM-sIgD levels might be associated with low-affinity OVM-sIgE levels and reflect the replacement of high-affinity with low-affinity OVM-specific IgE as children outgrow egg allergy, resulting in hypo-responsiveness to OVM.

A recent study found that OVM-sIgE avidity was more effective at differentiating clinically reactive egg-allergic patients from those tolerant of heated egg compared to EW-sIgE.⁴ We found that the ratio of OVM-sIgE to OVM-sIgD or sIgG4 in the CAE group was significantly higher compared to the PAE, OGE, and NEA groups (Figure 2). Receiver-operating analysis revealed that the ratio of OVM-sIgE to OVM-sIgD discriminated non-tolerant from partially tolerant egg-allergic patients with the largest area under the curve (AUC = 0.965) compared with levels of OVM-sIgE or the ratio of OVM-sIgE to OVM-sIgG4. The optimal cutoff for the ratio of OVM-sIgE to OVM-sIgD had 86.5% sensitivity and 96.4% specificity to identify high-risk subjects (Table S2).

There are several limitations to this study. First, there was a small number of patients. Second, children were only challenged with heated egg and were instructed to avoid egg of any form if they tested positive with less than 1/32 cooked whole egg. Finally, there was a lack of trajectory of sIgD levels during natural tolerance development.

In conclusion, the ratio of OVM-sIgE to OVM-sIgD is a useful marker to identify high-risk egg-allergic patients capable of ingesting a low dose of cooked whole egg who might be a good candidate for low-dose oral food challenge tests.